

WHAT IS CLAIMED IS:

1. A method of treating a disease mediated by p38 within a host, said method comprising administering to said host a compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein

D is $-\text{NH}-\text{C}(\text{O})-\text{NH}-$,

A is a substituted moiety of up to 40 carbon atoms of the formula: $-\text{L}-(\text{M}-\text{L}^1)_q$, where L is a 5 or 6 membered cyclic structure bound directly to D, L^1 comprises a substituted cyclic moiety having at least 5 members, M is a bridging group having at least one atom, q is an integer of from 1-3; and each cyclic structure of L and L^1 contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, and

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur,

wherein L^1 is substituted by at least one substituent selected from the group consisting of $-\text{SO}_2\text{R}_x$, $-\text{C}(\text{O})\text{R}_x$ and $-\text{C}(\text{NR}_y)\text{R}_z$,

R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo;

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

R_x is R_z or NR_aR_b where R_a and R_b are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

$-\text{OSi}(\text{R}_f)_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

c) one of R_a or R_b is $-\text{C}(\text{O})-$, a C_1 - C_5 divalent alkylene group or a substituted C_1 - C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1 - C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

where B is substituted, L is substituted or L^1 is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and W_n , where n is 0-3;

wherein each W is independently selected from the group consisting of $-\text{CN}$, $-\text{CO}_2\text{R}^7$, $-\text{C}(\text{O})\text{NR}^7\text{R}^7$, $-\text{C}(\text{O})-\text{R}^7$, $-\text{NO}_2$, $-\text{OR}^7$, $-\text{SR}^7$, $-\text{NR}^7\text{R}^7$, $-\text{NR}^7\text{C}(\text{O})\text{OR}^7$, $-\text{NR}^7\text{C}(\text{O})\text{R}^7$, $-\text{Q}-\text{Ar}$, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of $-\text{CN}$, $-\text{CO}_2\text{R}^7$, $-\text{C}(\text{O})\text{R}^7$, $-\text{C}(\text{O})\text{NR}^7\text{R}^7$, $-\text{OR}^7$, $-\text{SR}^7$, $-\text{NR}^7\text{R}^7$, $-\text{NO}_2$, $-\text{NR}^7\text{C}(\text{O})\text{R}^7$, $-\text{NR}^7\text{C}(\text{O})\text{OR}^7$ and

halogen up to per-halo; with each R^7 independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen,

wherein Q is -O-, -S-, -N(R^7)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R^7)-, -O(CH₂)_m- CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R^7)(CH₂)_m-, where m= 1-3, and X^a is halogen; and

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of -CN, -CO₂R⁷, -C(O)R⁷, -C(O)NR⁷R⁷, -NO₂, -OR⁷, -SR⁷, -NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of -CN, -CO₂R⁷, -COR⁷, -C(O)NR⁷R⁷, -OR⁷, -SR⁷, -NO₂, -NR⁷R⁷, -NR⁷C(O)R⁷, and -NR⁷C(O)OR⁷, with R⁷ as defined above.

2. A method as in claim 1 for the treatment of a cancerous cell growth mediated by p38 kinase.

3. A method as in claim 1 for the treatment of a disease other than cancer.

4. A method as in claim 1 wherein the condition within a host treated by administering a compound of formula I is rheumatoid arthritis, osteoarthritis, septic arthritis, tumor metastasis, periodontal disease, corneal ulceration, proteinuria, coronary thrombosis from atherosclerotic plaque, aneurysmal aortic, birth control, dystrophic epidermolysis bullosa, degenerative cartilage loss following traumatic joint injury, osteopenias mediated by MMP activity, temporomandibular joint disease or demyelating disease of the nervous system.

5. A method as in claim 1 wherein the condition within a host treated by administering a compound of formula I is rheumatic fever, bone resorption, postmenopausal osteoporosis, sepsis, gram negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, systemic inflammatory response syndrome, inflammatory bowel disease (Crohn's disease and ulcerative colitis), Jarisch-Herxheimer reaction,

asthma, adult respiratory distress syndrome, acute pulmonary fibrotic disease, pulmonary sarcoidosis, allergic respiratory disease, silicosis, coal worker's pneumoconiosis, alveolar injury, hepatic failure, liver disease during acute inflammation, severe alcoholic hepatitis, malaria (*Plasmodium falciparum* malaria and cerebral malaria), non-insulin-dependent diabetes mellitus (NIDDM), congestive heart failure, damage following heart disease, atherosclerosis, Alzheimer's disease, acute encephalitis, brain injury, multiple sclerosis (demyelation and oligiodendrocyte loss in multiple sclerosis), advanced cancer, lymphoid malignancy, pancreatitis, impaired wound healing in infection, inflammation and cancer, myelodysplastic syndromes, systemic lupus erythematosus, biliary cirrhosis, bowel necrosis, psoriasis, radiation injury/ toxicity following administration of monoclonal antibodies, host-versus-graft reaction (ischemia reperfusion injury and allograft rejections of kidney, liver, heart, and skin), lung allograft rejection (obliterative bronchitis) or complications due to total hip replacement.

6. A method as in claim 1 wherein the condition within a host treated by administering a compound of formula I is an infectious disease selected from the group consisting of tuberculosis, *Helicobacter pylori* infection during peptic ulcer disease, Chaga's disease resulting from *Trypanosoma cruzi* infection, effects of Shiga-like toxin resulting from *E. coli* infection, effects of enterotoxin A resulting from *Staphylococcus* infection, meningococcal infection, and infections from *Borrelia burgdorferi*, *Treponema pallidum*, cytomegalovirus, influenza virus, Theiler's encephalomyelitis virus, and the human immunodeficiency virus (HIV).

7. A method as in claim 1 wherein M is one or more bridging groups selected from the group consisting of -O-, -S-, -N(R⁷)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R⁷)-, -O(CH₂)_m-CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R⁷)(CH₂)_m-, where m= 1-3, X^a is halogen and R⁷ is as defined in claim 1.

8. A method as in claim 7, wherein said substituted cyclic moiety L¹ is phenyl, pyridyl or pyrimidinyl.

9. A method of claim 1 wherein L^1 is substituted by $-C(O)R_x$ or $-SO_2R_x$, wherein R_x is NR_aR_b .

10. A method of treating a disease mediated by p38 within a host, said method comprising administering to said host a compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein

D is $-NH-C(O)-NH-$,

A is a substituted moiety of up to 40 carbon atoms of the formula: $-L-(M-L^1)_q$, where L is a 6 membered aryl moiety or a 6 membered hetaryl moiety bound directly to D, L^1 comprises a substituted cyclic moiety having at least 5 members, M is a bridging group having at least one atom, q is an integer of from 1-3; and each cyclic structure of L and L^1 contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, and

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur,

wherein L^1 is substituted by at least one substituent selected from the group consisting of $-SO_2R_x$, $-C(O)R_x$ and $-C(NR_y)R_z$,

R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo;

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

R_x is R_z or NR_aR_b where R_a and R_b are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

-OSi(R_f)₃ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

c) one of R_a or R_b is -C(O)-, a C₁-C₅ divalent alkylene group or a substituted C₁-C₅ divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C₁-C₅ divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

where B is substituted, L is substituted or L¹ is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and W_n, where n is 0-3;

wherein each W is independently selected from the group consisting of -CN, -CO₂R⁷, -C(O)NR⁷R⁷, -C(O)-R⁷, -NO₂, -OR⁷, -SR⁷, -NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, -Q-Ar, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of -CN, -CO₂R⁷, -C(O)R⁷, -C(O)NR⁷R⁷, -OR⁷, -SR⁷, -NR⁷R⁷, -NO₂, -NR⁷C(O)R⁷, -NR⁷C(O)OR⁷ and

halogen up to per-halo; with each R^7 independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen,

wherein Q is -O-, -S-, -N(R^7)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R^7)-, -O(CH₂)_m- CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R^7)(CH₂)_m-, where m= 1-3, and X^a is halogen;

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of -CN, -CO₂R⁷, -C(O)R⁷, -C(O)NR⁷R⁷, -NO₂, -OR⁷, -SR⁷, -NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of -CN, -CO₂R⁷, -COR⁷, -C(O)NR⁷R⁷, -OR⁷, -SR⁷, -NO₂, -NR⁷R⁷, -NR⁷C(O)R⁷, and -NR⁷C(O)OR⁷; and

wherein M is one or more bridging groups selected from the group consisting of -O-, -S-, -N(R^7)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R^7)-, -O(CH₂)_m- CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R^7)(CH₂)_m-, where m= 1-3, X^a is halogen and R⁷ is as defined above.

11. A method of treating a disease mediated by p38 within a host, said method comprising administering to said host a compound of Formula I :



or a pharmaceutically acceptable salt thereof, wherein

D is -NH-C(O)-NH-,

A is a substituted moiety of up to 40 carbon atoms of the formula: -L-(M-L¹)_q, where L is a substituted or unsubstituted phenyl or pyridine moiety bound directly to D, L¹ comprises a substituted phenyl, pyridine or pyrimidinyl moiety, M is a bridging group having at least one atom, q is an integer of from 1-3; and

B is a substituted or unsubstituted phenyl or pyridine group bound directly to D,

wherein L^1 is substituted by at least one substituent selected from the group consisting of $-SO_2R_x$, $-C(O)R_x$ and $-C(NR_y)R_z$,

R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo;

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

R_x is R_z or NR_aR_b where R_a and R_b are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

$-OSi(R_f)_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

c) one of R_a or R_b is $-C(O)-$, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

where B is substituted, L is substituted or L^1 is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and W_n , where n is 0-3;

wherein each W is independently selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)NR^7R^7$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, $-Q-Ar$, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NO_2$, $-NR^7C(O)R^7$, $-NR^7C(O)OR^7$ and halogen up to per-halo; with each R^7 independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen,

wherein Q is $-O-$, $-S-$, $-N(R^7)-$, $-(CH_2)_m-$, $-C(O)-$, $-CH(OH)-$, $-(CH_2)_mO-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^7)-$, $-O(CH_2)_m-$, $-CHX^a-$, $-CX^a_2-$, $-S-(CH_2)_m-$ and $-N(R^7)(CH_2)_m-$, where $m=1-3$, and X^a is halogen;

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{n1} , wherein $n1$ is 0 to 3 and each Z is independently selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of $-CN$, $-CO_2R^7$, $-COR^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NO_2$, $-NR^7R^7$, $-NR^7C(O)R^7$, and $-NR^7C(O)OR^7$; with R^7 is as defined above; and

wherein M is one or more bridging groups selected from the group consisting of -O-, -S-, -N(R⁷)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R⁷)-, -O(CH₂)_m-CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R⁷)(CH₂)_m-, where m= 1-3, X^a is halogen and R⁷ is as defined above.

12. A method for the treatment of a disease mediated by p38 kinase ^{to which} other than cancer] which comprises administering a compound selected from the group consisting of the 3-tert butyl phenyl ureas:

N-(3-tert-butylphenyl)-*N'*-(4-(3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea and
N-(3-tert-butylphenyl)-*N'*-(4-(4-acetylphenoxy)phenyl) urea;

the 5-tert-butyl-2-methoxyphenyl ureas:

N-(5-tert-butyl-2-methoxyphenyl)-*N'*-(4-(1,3-dioxoisindolin-5-yloxy)phenyl) urea,
N-(5-tert-butyl-2-methoxyphenyl)-*N'*-(4-(1-oxoisindolin-5-yloxy)phenyl) urea,
N-(5-tert-butyl-2-methoxyphenyl)-*N'*-(4-(4-methoxy-3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea and
N-(5-tert-butyl-2-methoxyphenyl)-*N'*-(4-(3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea;

the 2-methoxy-5-trifluoromethylphenyl ureas:

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-carbamoyl-4-pyridyloxy)phenyl) urea,
N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,
N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea,
N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,
N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridylthio)phenyl) urea,

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(2-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea and
N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(3-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea;

the 4-chloro-3-(trifluoromethyl)phenyl ureas:

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-carbamoyl-4-pyridyloxy)phenyl) urea,
N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,
N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea and
N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea;

the 4-bromo-3-(trifluoromethyl)phenyl ureas:

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,
N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,
N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridylthio)phenyl) urea,
N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(2-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea and
N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(3-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea; and

the 2-methoxy-4-chloro-5-(trifluoromethyl)phenyl ureas:

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,
N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(2-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea and
N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(3-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea.

13. A pharmaceutical composition for the treatment of a disease within a host mediated by p38 comprising a compound of Formula I,



or a pharmaceutically acceptable salt thereof, in an amount effective to treat a disease mediated by p38 and a physiologically acceptable carrier:

wherein

D is $-NH-C(O)-NH-$,

A is a substituted moiety of up to 40 carbon atoms of the formula: $-L-(M-L^1)_q$, where L is a 5 or 6 membered cyclic structure bound directly to D, L^1 comprises a substituted cyclic moiety having at least 5 members, M is a bridging group having at least one atom, q is an integer of from 1-3; and each cyclic structure of L and L^1 contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, and

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur,

wherein L^1 is substituted by at least one substituent selected from the group consisting of $-SO_2R_x$, $-C(O)R_x$ and $-C(NR_y)R_z$,

R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo,

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

R_x is R_z or NR_aR_b where R_a and R_b are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

-OSi(R_f)₃ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

c) one of R_a or R_b is -C(O)-, a C₁-C₅ divalent alkylene group or a substituted C₁-C₅ divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C₁-C₅ divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

where B is substituted, L is substituted or L¹ is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and W_n, where n is 0-3;

wherein each W is independently selected from the group consisting of -CN, -CO₂R⁷, -C(O)NR⁷R⁷, -C(O)-R⁷, -NO₂, -OR⁷, -SR⁷, -NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, -Q-Ar, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of -CN, -CO₂R⁷, -C(O)R⁷, -C(O)NR⁷R⁷, -OR⁷, -SR⁷, -NR⁷R⁷, -NO₂, -NR⁷C(O)R⁷, -NR⁷C(O)OR⁷ and halogen up to per-halo; with each R⁷ independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen,

wherein Q is -O-, -S-, -N(R⁷)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R⁷)-, -O(CH₂)_m-CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R⁷)(CH₂)_m-, where m= 1-3, and X^a is halogen; and

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of -CN, -CO₂R⁷, -C(O)R⁷, -C(O)NR⁷R⁷, -NO₂, -OR⁷, -SR⁷, -NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of -CN, -CO₂R⁷, -COR⁷, -C(O)NR⁷R⁷, -OR⁷, -SR⁷, -NO₂, -NR⁷R⁷, -NR⁷C(O)R⁷, and -NR⁷C(O)OR⁷, with R⁷ as defined above.

14. A pharmaceutical composition as in claim 13 wherein:

R_y is hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl having 0-3 heteroatoms, C₂₋₁₀ alkenyl, C₁₋₁₀ alkenoyl, C₆₋₁₂ aryl, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₇₋₂₄ aralkyl, C₇₋₂₄ alkaryl, substituted C₁₋₁₀ alkyl, substituted C₁₋₁₀ alkoxy, substituted C₃₋₁₀ cycloalkyl having 0-3 heteroatoms selected from N, S and O,

substituted C₆-C₁₄ aryl, substituted C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, substituted C₇₋₂₄ alkaryl or substituted C_{7-C24} aralkyl, where R_y is a substituted group, it is substituted by halogen up to per halo,

R_z is hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C₃₋₁₀ cycloalkyl having 0-3 heteroatom, C₂₋₁₀ alkenyl, C₁₋₁₀ alkenoyl, C₆₋₁₂ aryl, C_{3-C12} hetaryl having 1-3 heteroatoms selected from, S, N and O, C₇₋₂₄ alkaryl, C₇₋₂₄ aralkyl, substituted C₁₋₁₀ alkyl, substituted C₁₋₁₀ alkoxy, substituted C_{6-C14} aryl, substituted C_{3-C10} cycloalkyl having 0-3 heteroatoms selected from S, N and O, substituted C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, O and S, substituted C₇₋₂₄ alkaryl or substituted C_{7-C24} aralkyl where R_z is a substituted group, it is substituted by halogen up to per halo, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₁₋₆ halo substituted alkyl up to per halo alkyl, C_{6-C12} halo substituted aryl up to per halo aryl, C_{3-C12} halo substituted cycloalkyl up to per halo cycloalkyl having 0-3 heteroatoms selected from N, S and O, halo substituted C_{3-C12} hetaryl up to per halo hetaryl having 1-3 heteroatoms selected from N, S and O, halo substituted C_{7-C24} aralkyl up to per halo aralkyl, halo substituted C_{7-C24} alkaryl up to per halo alkaryl, and -C(O)R_g,

R_a and R_b are,

a) independently hydrogen,

a carbon based moiety selected from the group consisting of C_{1-C10} alkyl, C_{1-C10} alkoxy, C₃₋₁₀ cycloalkyl, C₂₋₁₀ alkenyl, C₁₋₁₀ alkenoyl, C₆₋₁₂ aryl, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from O, N and S, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from N, S and O, C₇₋₂₄ aralkyl, C_{7-C24} alkaryl, substituted C₁₋₁₀ alkyl, substituted C₁₋₁₀ alkoxy, substituted C₃₋₁₀ cycloalkyl, having 0-3 heteroatoms selected from N, S and O, substituted C₆₋₁₂ aryl, substituted C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, substituted C₇₋₂₄ aralkyl, substituted C₇₋₂₄ alkaryl, where R_a and R_b are a substituted group, they are substituted by halogen up to per halo, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N,

C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C₁₋₆ halo substituted alkyl up to per halo alkyl, C_{6-C12} halo substituted aryl up to per halo aryl, C_{3-C12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_{3-C12} hetaryl up to per halo heteraryl, halo substituted C_{7-C24} aralkyl up to per halo aralkyl, halo substituted C_{7-C24} alkaryl up to per halo alkaryl, and -C(O)R_g; or

-OSi(R_f)₃ where R_f is hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, C_{3-C10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₆₋₁₂ aryl, C_{3-C12} hetaryl having 1-3 heteroatoms selected from O, S and N, C₇₋₂₄ aralkyl, substituted C₁₋₁₀ alkyl, substituted C_{1-C10} alkoxy, substituted C_{3-C12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, substituted C_{3-C12} heteraryl having 1-3 heteroatoms selected from O, S, and N, substituted C₆₋₁₂ aryl, and substituted C₇₋₂₄ alkaryl, where R_f is a substituted group it is substituted halogen up to per halo, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C_{7-C24} alkaryl, C_{7-C24} aralkyl, C₁₋₆ halo substituted alkyl up to per halo alkyl, C_{6-C12} halo substituted aryl up to per halo aryl, C_{3-C12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_{3-C12} hetaryl up to per halo heteraryl, halo substituted C_{7-C24} aralkyl up to per halo aralkyl, halo substituted C_{7-C24} alkaryl up to per halo alkaryl, and -C(O)R_g, or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O with substituents selected from the group consisting of halogen up to per halo, hydroxy, C₁₋₁₀ alkyl, C₃₋₁₂ cycloalkyl having 0-3 heteroatoms selected from O, S and N, C₃₋₁₂ hetaryl having 1-3 heteroatoms selected from N, S and O, C₁₋₁₀ alkoxy, C₆₋₁₂ aryl, C_{7-C24} alkaryl, C_{7-C24} aralkyl, halo substituted C₁₋₆ alkyl up to per halo alkyl, halo substituted C_{6-C12} aryl up to per halo aryl, halo substituted C_{3-C12} cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_{3-C12} hetaryl up to per halo heteraryl, halo substituted C_{7-C24} aralkyl up to per halo aralkyl, halo substituted C_{7-C24} alkaryl up to per halo alkaryl, and -C(O)R_g, or

c) one of R_a or R_b is $-C(O)-$, a C_1-C_5 divalent alkylene group or a substituted C_1-C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1-C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, C_{1-10} alkyl, C_{3-12} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{3-12} hetaryl having 1-3 heteroatoms selected from N, S and O, C_{1-10} alkoxy, C_{6-12} aryl, C_7-C_{24} alkaryl, C_7-C_{24} aralkyl, C_{1-6} halo substituted alkyl up to per halo alkyl, C_{6-12} halo substituted aryl up to per halo aryl, C_3-C_{12} halo substituted cycloalkyl having 0-3 heteroatoms selected from N, S and O, up to per halo cycloalkyl, halo substituted C_3-C_{12} hetaryl up to per halo heteraryl, halo substituted C_7-C_{24} aralkyl up to per halo aralkyl, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, and $-C(O)R_g$,

where R_g is C_{1-10} alkyl, $-CN$, $-CO_2R_d$, $-OR_d$, $-SR_d$, $-NO_2$, $-C(O)R_e$, $-NR_dR_e$, $-NR_dC(O)OR_e$ and $-NR_dC(O)R_e$, and R_d and R_e are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{1-10} alkoxy, C_{3-10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, C_{6-12} aryl, C_3-C_{12} hetaryl with 1-3 heteroatoms selected from O, N and S and C_7-C_{24} aralkyl, C_7-C_{24} alkaryl, up to per halo substituted C_1-C_{10} alkyl, up to per halo substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, up to per halo substituted C_6-C_{14} aryl, up to per halo substituted C_3-C_{12} hetaryl having 1-3 heteroatoms selected from O, N, and S, halo substituted C_7-C_{24} alkaryl up to per halo alkaryl, and up to per halo substituted C_7-C_{24} aralkyl,

W is independently selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)NR^7R^7$, $-C(O)-R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_2-C_{10} alkenyl, C_1-C_{10} alkenoyl, C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, S and N, C_{6-14} aryl, C_7-C_{24} alkaryl, C_7-C_{24} aralkyl, C_3-C_{12} heteroaryl having 1-3 heteroatoms selected from O, N and S, C_4-C_{23} alkheteroaryl having 1-3 heteroatoms selected from O, N and S, substituted C_1-C_{10} alkyl, substituted C_1-C_{10} alkoxy, substituted C_2-C_{10} alkenyl, substituted C_1-C_{10} alkenoyl, substituted C_3-C_{10} cycloalkyl having 0-3 heteroatoms selected from O, N and S, substituted C_{6-12} aryl, substituted C_3-C_{12} hetaryl having 1-3 heteroatoms selected from O, N and S, substituted

C₇-C₂₄ aralkyl, substituted C₇-C₂₄ alkaryl, substituted C₄-C₂₃ alkheteroaryl having 1-3 heteroatoms selected from O, N and S, and -Q-Ar;

R⁷ is independently selected from H, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, C₂-C₁₀ alkenyl, C₁-C₁₀ alkenoyl, C₃-C₁₀ cycloalkyl having 0-3 heteroatoms selected from O, N and S, C₆-C₁₄ aryl, C₃-C₁₃ hetaryl having 1-3 heteroatoms selected from O, N and S, C₇-C₁₄ alkaryl, C₇-C₂₄ aralkyl, C₄-C₂₃ alkheteroaryl having 1-3 heteroatoms selected from O, N and S, up to per-halosubstituted C₁-C₁₀ alkyl, up to per-halosubstituted C₃-C₁₀ cycloalkyl having 0-3 heteroatoms selected from O, N and S, up to per-halosubstituted C₆-C₁₄ aryl, up to per-halosubstituted C₃-C₁₃ hetaryl having 1-3 heteroatoms selected from O, N and S, up to per-halosubstituted C₇-C₂₄ aralkyl, up to per-halosubstituted C₇-C₂₄ alkaryl, and up to per-halosubstituted C₄-C₂₃ alkheteroaryl; and

each Z is independently selected from the group consisting of -CN, -CO₂R⁷, -C(O)R⁷, -C(O)NR⁷R⁷, -NO₂, -OR⁷, -SR⁷, -NR⁷R⁷, -NR⁷C(O)OR⁷, -NR⁷C(O)R⁷, C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, C₂-C₁₀ alkenyl, C₁-C₁₀ alkenoyl, C₃-C₁₀ cycloalkyl having 0-3 heteroatoms selected from O, N and S, C₆-C₁₄ aryl, C₃-C₁₃ hetaryl having 1-3 heteroatoms selected from O, N and S, C₇-C₂₄ alkaryl, C₇-C₂₄ aralkyl, C₄-C₂₃ alkheteroaryl having 1-3 heteroatoms selected from O, N and S, substituted C₁-C₁₀ alkyl, substituted C₁-C₁₀ alkoxy, substituted C₂-C₁₀ alkenyl, substituted C₁-C₁₀ alkenoyl, substituted C₃-C₁₀ cycloalkyl having 0-3 heteroatoms selected from O, N and S, substituted C₆-C₁₂ aryl, substituted C₇-C₂₄ alkaryl, substituted C₇-C₂₄ aralkyl and substituted C₄-C₂₃ alkheteroaryl having 1-3 heteroatoms selected from O, N and S; wherein if Z is a substituted group, the one or more substituents are selected from the group consisting of -CN, -CO₂R⁷, -COR⁷, -C(O)NR⁷R⁷, -OR⁷, -SR⁷, -NO₂, -NR⁷R⁷, -NR⁷C(O)R⁷, and -NR⁷C(O)OR⁷.

15. A pharmaceutical composition as in claim 13 wherein M is one or more bridging groups selected from the group consisting of -O-, -S-, -N(R⁷)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R⁷)-, -O(CH₂)_m-CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R⁷)(CH₂)_m-, where m = 1-3, X^a is halogen and R⁷ is as defined in claim 13.

16. A pharmaceutical composition as in claim 13 wherein the cyclic structures of B and L bound directly to D are not substituted in the ortho position by -OH.

17. A pharmaceutical composition as in claim 13 wherein the cyclic structures of B and L bound directly to D are not substituted in the ortho position by a moiety having an ionizable hydrogen and a pKa of 10 or less.

18. A pharmaceutical composition as in claim 13 wherein B of Formula I is a substituted or unsubstituted six member aryl moiety or six member hetaryl moiety, said hetaryl moiety having 1 to 4 members selected from the group of hetaryl atoms consisting of nitrogen, oxygen and sulphur with the balance of the hetaryl moiety being carbon.

19. A pharmaceutical composition as in claim 13 wherein B of Formula I is an unsubstituted phenyl group, an unsubstituted pyridyl group, an unsubstituted pyrimidinyl group, a phenyl group substituted by a substituent selected from the group consisting of halogen and W_n wherein W and n are as defined in claim 13, a pyrimidinyl group substituted by a substituted selected from halogen and W_n, wherein W and n are as defined in Claim 13, or a pyridyl group substituted by a substituent selected from the group consisting of halogen and W_n wherein W and n are as defined in claim 13.

20. A pharmaceutical composition as in claim 13, wherein L, the six member cyclic structure bound directly to D, is a substituted or unsubstituted 6 member aryl moiety or a substituted or unsubstituted 6 member hetaryl moiety, wherein said hetaryl moiety has 1 to 4 members selected from the group of heteroatoms consisting of nitrogen, oxygen and sulphur with the balance of said hetaryl moiety being carbon, wherein the one or more substituents are selected from the group consisting of halogen and W_n, wherein W and n are as defined in claim 13.

21. A pharmaceutical composition as in claim 13, wherein L, the 6 member cyclic structure bound directly to D, is a substituted phenyl, unsubstituted phenyl, substituted pyridyl, unsubstituted pyridyl group, unsubstituted pyrimidinyl or substituted pyrimidinyl.

22. A pharmaceutical composition as in claim 13, wherein said substituted cyclic moiety L¹ comprises a 5 to 6 membered aryl moiety or hetaryl moiety, wherein

said heteraryl moiety comprises 1 to 4 members selected from the group of heteroatoms consisting of nitrogen, oxygen and sulphur.

23. A pharmaceutical composition as in claim 13, wherein said substituted cyclic moiety L^1 is phenyl, pyridyl or pyrimidinyl and M is one or more bridging groups selected from the group consisting of -O-, -S-, -N(R⁷)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R⁷)-, -O(CH₂)_m-CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R⁷)(CH₂)_m-, where m= 1-3, X^a is halogen and R⁷ is hydrogen or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen up to pre halo.

24. A pharmaceutical composition as in claim 13 wherein L¹ is additionally substituted 1 to 3 times by one or more substituents selected from the group consisting of C₁-C₁₀ alkyl, up to per halo substituted C₁-C₁₀ alkyl, -CN, -OH, halogen, C₁-C₁₀ alkoxy and up to per halo substituted C₁-C₁₀ alkoxy.

25. A pharmaceutical composition as in claim 13 wherein L¹ is substituted by -C(O)R_x.

26. A pharmaceutical composition as in claim 13 wherein L¹ is substituted by -C(O)R_x or -SO₂R_x, wherein R_x is NR_aR_b.

27. A pharmaceutical composition for the treatment of a disease within a host mediated by p38 comprising a compound of Formula I:



or a pharmaceutically acceptable salt thereof, in an amount effective to treat a disease mediated by p38 and a physiologically acceptable carrier, wherein

D is -NH-C(O)-NH-,

A is a substituted moiety of up to 40 carbon atoms of the formula: -L-(M-L¹)_q, where L is a 6 membered aryl moiety or a 6 membered hetaryl moiety bound directly to D, L¹ comprises a substituted cyclic moiety having at least 5 members, M is a bridging group having at least one atom, q is an integer of from 1-3; and each cyclic structure of L and L¹ contains 0-4 members of the group consisting of nitrogen, oxygen and sulfur, and

B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur,

wherein L^1 is substituted by at least one substituent selected from the group consisting of $-SO_2R_x$, $-C(O)R_x$ and $-C(NR_y)R_z$,

R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo,

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

R_x is R_z or NR_aR_b where R_a and R_b are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

$-OSi(R_f)_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

c) one of R_a or R_b is $-C(O)-$, a C_1 - C_5 divalent alkylene group or a substituted C_1 - C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1 - C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

where B is substituted, L is substituted or L^1 is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and W_n , where n is 0-3;

wherein each W is independently selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)NR^7R^7$, $-C(O)R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, $-Q-Ar$, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NO_2$, $-NR^7C(O)R^7$, $-NR^7C(O)OR^7$ and halogen up to per-halo; with each R^7 independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen,

wherein Q is $-O-$, $-S-$, $-N(R^7)-$, $-(CH_2)_m-$, $-C(O)-$, $-CH(OH)-$, $-(CH_2)_mO-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^7)-$, $-O(CH_2)_m-$, CHX^a- , $-CX^a_2-$, $-S-(CH_2)_m-$ and $-N(R^7)(CH_2)_m-$, where $m=1-3$, and X^a is halogen;

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{n1} , wherein $n1$ is 0 to 3 and each Z is independently selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents are selected from the group consisting of $-CN$, $-CO_2R^7$, $-COR^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NO_2$, $-NR^7R^7$, $-NR^7C(O)R^7$, and $-NR^7C(O)OR^7$ with R^7 as defined above; and

wherein M is one or more bridging groups selected from the group consisting of -O-, -S-, -N(R⁷)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R⁷)-, -O(CH₂)_m-CHX^a-, -CX^a₂-, -S-(CH₂)_m- and -N(R⁷)(CH₂)_m-, where m= 1-3, X^a is halogen and R⁷ is as defined above.

28. A pharmaceutical composition for the treatment of a disease within a host mediated by p38 comprising a compound of Formula I:



or a pharmaceutically acceptable salt thereof, in an amount effective to treat a disease mediated by p38 and a physiologically acceptable carrier, wherein

D is -NH-C(O)-NH-,

A is a substituted moiety of up to 40 carbon atoms of the formula: -L-(M-L¹)_q, where L is a substituted or unsubstituted phenyl or pyridyl moiety bound directly to D, L¹ comprises a substituted phenyl, pyridyl or pyrimidinyl moiety, M is a bridging group having at least one atom, q is an integer of from 1-3; and

B is a substituted or unsubstituted phenyl or pyridine group bound directly to D,

wherein L¹ is substituted by at least one substituent selected from the group consisting of -SO₂R_x, -C(O)R_x and -C(NR_y)R_z,

R_y is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally halosubstituted, up to per halo, and ;

R_z is hydrogen or a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

R_x is R_z or NR_aR_b where R_a and R_b are

a) independently hydrogen,

a carbon based moiety of up to 30 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen, or

$-\text{OSi}(\text{R}_f)_3$ where R_f is hydrogen or a carbon based moiety of up to 24 carbon atoms optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen, hydroxy and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

b) R_a and R_b together form a 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O, or a substituted 5-7 member heterocyclic structure of 1-3 heteroatoms selected from N, S and O substituted by halogen, hydroxy or carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen; or

c) one of R_a or R_b is $-\text{C}(\text{O})-$, a C_1 - C_5 divalent alkylene group or a substituted C_1 - C_5 divalent alkylene group bound to the moiety L to form a cyclic structure with at least 5 members, wherein the substituents of the substituted C_1 - C_5 divalent alkylene group are selected from the group consisting of halogen, hydroxy, and carbon based substituents of up to 24 carbon atoms, which optionally contain heteroatoms selected from N, S and O and are optionally substituted by halogen;

where B is substituted, L is substituted or L^1 is additionally substituted, the substituents are selected from the group consisting of halogen, up to per-halo, and W_n , where n is 0-3;

wherein each W is independently selected from the group consisting of $-\text{CN}$, $-\text{CO}_2\text{R}^7$, $-\text{C}(\text{O})\text{NR}^7\text{R}^7$, $-\text{C}(\text{O})-\text{R}^7$, $-\text{NO}_2$, $-\text{OR}^7$, $-\text{SR}^7$, $-\text{NR}^7\text{R}^7$, $-\text{NR}^7\text{C}(\text{O})\text{OR}^7$, $-\text{NR}^7\text{C}(\text{O})\text{R}^7$, $-\text{Q}-\text{Ar}$, and carbon based moieties of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents independently selected from the group consisting of $-\text{CN}$, $-\text{CO}_2\text{R}^7$, $-\text{C}(\text{O})\text{R}^7$, $-\text{C}(\text{O})\text{NR}^7\text{R}^7$, $-\text{OR}^7$, $-\text{SR}^7$, $-\text{NR}^7\text{R}^7$, $-\text{NO}_2$, $-\text{NR}^7\text{C}(\text{O})\text{R}^7$, $-\text{NR}^7\text{C}(\text{O})\text{OR}^7$ and

halogen up to per-halo; with each R^7 independently selected from H or a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by halogen,

wherein Q is $-O-$, $-S-$, $-N(R^7)-$, $-(CH_2)_m-$, $-C(O)-$, $-CH(OH)-$, $-(CH_2)_mO-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^7)-$, $-O(CH_2)_m-$, $-CHX^a-$, $-CX^a_2-$, $-S-(CH_2)_m-$ and $-N(R^7)(CH_2)_m-$, where $m=1-3$, and X^a is halogen;

Ar is a 5- or 6-member aromatic structure containing 0-2 members selected from the group consisting of nitrogen, oxygen and sulfur, which is optionally substituted by halogen, up to per-halo, and optionally substituted by Z_{n1} , wherein $n1$ is 0 to 3 and each Z is independently selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)R^7$, $-C(O)NR^7R^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, and a carbon based moiety of up to 24 carbon atoms, optionally containing heteroatoms selected from N, S and O and optionally substituted by one or more substituents selected from the group consisting of $-CN$, $-CO_2R^7$, $-COR^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NO_2$, $-NR^7R^7$, $-NR^7C(O)R^7$, and $-NR^7C(O)OR^7$ with R^7 as defined above; and

wherein M is one or more bridging groups selected from the group consisting of $-O-$, $-S-$, $-N(R^7)-$, $-(CH_2)_m-$, $-C(O)-$, $-CH(OH)-$, $-(CH_2)_mO-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^7)-$, $-O(CH_2)_m-$, $-CHX^a-$, $-CX^a_2-$, $-S-(CH_2)_m-$ and $-N(R^7)(CH_2)_m-$, where $m=1-3$, X^a is halogen and R^7 is as defined above.

29. A pharmaceutical composition as in claim 27 wherein the cyclic structures of B and L bound directly to D are not substituted in the ortho position by-OH.

30. A pharmaceutical composition as in claim 27, wherein the cyclic structures of B and L bound directly to D are not substituted in the ortho position by a moiety having an ionizable hydrogen and a pK_a of 10 or less.

31. A pharmaceutical composition as in claim 28, wherein the cyclic structures of B and L bound directly to D are not substituted in the ortho position by-OH.

32. A pharmaceutical composition as in claim 28 wherein the cyclic structures of B and L bound directly to D are not substituted in the ortho position by a moiety having an ionizable hydrogen and a pKa of 10 or less.

33. A pharmaceutical composition as in claim 27 wherein L^1 is substituted by $C(O)R_x$ or SO_2R_x , wherein R_x is NR_aR_b .

34. A pharmaceutical composition as in claim 28 wherein L^1 is substituted by $C(O)R_x$ or SO_2R_x , wherein R_x is NR_aR_b .

35. A pharmaceutical composition as in claim 13 which comprises a pharmaceutically acceptable salt of a compound of formula I selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

36. A pharmaceutical composition as in claim 27 which comprises a pharmaceutically acceptable salt of a compound of formula I selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic

acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

37. A pharmaceutical composition as in claim 28 which comprises a pharmaceutically acceptable salt of a compound of formula I selected from the group consisting of

a) basic salts of organic acids and inorganic acids selected from the group consisting of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluorosulphonic acid, benzenesulfonic acid, p-toluene sulphonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid; and

b) acid salts of organic and inorganic bases containing cations selected from the group consisting of alkaline cations, alkaline earth cations, the ammonium cation, aliphatic substituted ammonium cations and aromatic substituted ammonium cations.

38. A pharmaceutical composition for the treatment of a disease within a host mediated by p38 comprising a compound selected from the group consisting of the 3-tert butyl phenyl ureas:

N-(3-*tert*-butylphenyl)-*N'*-(4-(3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea and
N-(3-*tert*-butylphenyl)-*N'*-(4-(4-acetylphenoxy)phenyl) urea;

the 5-*tert*-butyl-2-methoxyphenyl ureas:

N-(5-*tert*-butyl-2-methoxyphenyl)-*N'*-(4-(1,3-dioxoisindolin-5-yloxy)phenyl) urea,
N-(5-*tert*-butyl-2-methoxyphenyl)-*N'*-(4-(1-oxoisindolin-5-yloxy)phenyl) urea,

N-(5-*tert*-butyl-2-methoxyphenyl)-*N'*-(4-(4-methoxy-3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea and
N-(5-*tert*-butyl-2-methoxyphenyl)-*N'*-(4-(3-(*N*-methylcarbamoyl)phenoxy)phenyl) urea;

the 2-methoxy-5-trifluoromethyl)phenyl ureas:

N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-carbamoyl-4-pyridyloxy)phenyl) urea,
N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,
N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea,
N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,
N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridylthio)phenyl) urea,
N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(2-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea and
N-(2-methoxy-5-(trifluoromethyl)phenyl)-*N'*-(3-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea;

the 4-chloro-3-(trifluoromethyl)phenyl ureas:

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-carbamoyl-4-pyridyloxy)phenyl) urea,
N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,
N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-carbamoyl-4-pyridyloxy)phenyl) urea and

N-(4-chloro-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea;

the 4-bromo-3-(trifluoromethyl)phenyl ureas:

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridylthio)phenyl) urea,

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(2-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea and

N-(4-bromo-3-(trifluoromethyl)phenyl)-*N'*-(3-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea; and

the 2-methoxy-4-chloro-5-(trifluoromethyl)phenyl ureas:

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy)phenyl) urea,

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(2-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea and

N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-*N'*-(3-chloro-4-(2-(*N*-methylcarbamoyl)(4-pyridyloxy))phenyl) urea, or a pharmaceutically acceptable salt thereof.